Decision Memo for Extracorporeal Photopheresis (CAG-00324R)

Decision Summary

The Centers for Medicare and Medicaid Services (CMS) has determined that extracorporeal photopheresis is reasonable and necessary for:

1. Patients with acute cardiac allograft rejection whose disease is refractory to standard immunosuppressive drug treatment; and

2. Patients with chronic graft versus host disease whose disease is refractory to standard immunosuppressive drug treatment.

CMS has determined that extracorporeal photopheresis is not reasonable and necessary for the treatment of bullous pemphigoid and pemphigus vulgaris.

All other indications remain non-covered.

Back to Top

Decision Memo

TO: Administrative File: CAG- 00324R
Extracorporeal Photopheresis

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SUBJECT: Decision Memorandum for Extracorporeal Photopheresis

DATE: December 19, 2006

I. Decision

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All other indications remain non-covered.

II. Background

A. Background of the Procedure

Extracorporeal photopheresis (also known as extracorporeal photochemotherapy) was first applied in the treatment of cutaneous T-cell lymphoma (CTCL) (Edelson, 1987). Over the years there has been an extension of extracorporeal photopheresis use in many diseases including rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, pemphigus vulgaris and more recently in solid organ allograft rejection and in graft versus host disease (Heshmati, 2003).

Extracorporeal photopheresis is a medical procedure in which a patient's white blood cells are exposed first to a drug called 8-methoxypsoralen (8-MOP) and then to ultraviolet A (UVA) light. The procedure starts with the removal of the patient's blood, which is centrifuged to isolate the white blood cells. The drug is typically administered directly to the white blood cells after they have been removed from the patient (referred to as ex vivo administration) but the drug can alternatively be administered directly to the patient before the white blood cells are withdrawn. After UVA light exposure, the treated white blood cells are then re-infused into the patient.

Extracorporeal photopheresis is usually performed on two consecutive days at four-week intervals with clinical evaluation at six months to determine response. The duration of treatment varies significantly depending on the medical condition being treated, and the patient's response to the treatments.

Today extracorporeal photopheresis is commonly administered via the UVAR® XTS™ system, which is an FDA-approved wholly-contained, automated processing system manufactured by Therakos, Inc. This system is a single unit that handles the collection of the patient's blood, the isolation of the white blood cells, and the ex vivo administration of 8-MOP and UVA. The UVAR® XTS™ system evolved from the FDA-approved UVAR® system, which used the oral formulation of 8-MOP. Other systems and protocols have been used to administer extracorporeal photopheresis, however. In this decision memorandum, CMS is evaluating the extracorporeal photopheresis procedure, and not a specific system for administering extracorporeal photopheresis.

The exact mechanism of action of extracorporeal photopheresis is still elusive (Edelson, 1987). The role of UVA is to activate the normally inert 8-MOP. The activated 8-MOP molecules bind with the DNA of the white blood cells, which kills the cells. The dead white blood cells, once reinfused into the patient, stimulate the multiple different cells and proteins of the patient's immune system in a series of cascading reactions. This activation of the immune system then impacts the medical condition being treated; however, the precise manner in which the medical condition is affected is still largely unknown but is believed to vary by condition (Therakos, Inc. 2006). Hence, extracorporeal photopheresis is a procedure that attempts to negatively impact the ability of specific immune cells to function but without inducing a general state of immunosuppression (Dall'Amico, 1995).

B. Disease Summary

1. Refractory Acute Cardiac Allograft Rejection

Cardiac transplantation is a procedure that involves the replacement of a failing heart with another heart from a suitable donor. One potential complication of cardiac transplantation is rejection of the transplanted heart. During rejection, the cardiac transplant recipient's immunological system produces cells and proteins that rightly recognize the transplanted heart as "foreign" and therefore attack it. Due to the serious nature of rejection, the patient is routinely started on immunosuppressive drug therapy immediately after the transplantation in an attempt to prevent the onset of rejection.

Although acute rejection of the transplanted heart can occur within days, months or years of transplantation (www.heart-transplant.org 2006), rejection most frequently occurs during the first month after transplantation (Patel, 2004). Histological rejection refers to the microscopic detection of the immunological attack on the heart during an episode of rejection. This type of rejection is associated primarily with specific immunologic cells called T lymphocytes and is referred to as cell-mediated rejection. A patient may or may not have symptoms in the presence of histological rejection. In fact, most patients with histological changes consistent with rejection have no change in heart function that could lead to symptoms (Hosenpud, 2005).

The chance that a patient may not have symptoms due to acute rejection mandates that routine testing be performed to detect the presence of rejection and to measure the effect of immunosuppressive drug treatment (Patel, 2004). An endomyocardial biopsy (EMB) is the gold standard for monitoring for the presence or absence as well as the severity of histological rejection. The degree of rejection present in the heart muscle has traditionally been graded as noted in the following table from the International Society of Heart and Lung Transplantation (ISHLT) (Billingham, 1990).

Billingham Classification for Grading Endomyocardial Biopsy[1]

Grade	Degree of Rejection
0	None
1	A: focal (perivascular or interstitial) infiltrate without necrosis B: diffuse but sparse infiltrate without necrosis
2	One focus only with aggressive infiltration and/or focal myocyte damage
3	A: multifocal aggressive infiltrates and/or myocyte damage B: diffuse inflammatory process with necrosis
4	Diffuse aggressive polymorphous +/- infiltrate +/- edema +/- hemorrhage +/- vasculitis, with necrosis

Once diagnosed, the management of acute rejection is dependent on the severity of the signs, symptoms, and changes in the histology (Patel, 2004). The majority of episodes of histological rejection are effectively treated with modification of the immunosuppressive drug therapy (Hosenpud, 2005). Using the Billingham classification, Grade 1A/B or 2 rejection without clinical signs or symptoms generally does not lead to a change in immunosuppression management. Steroids are typically administered for an asymptomatic Grade 3A/B rejection. Asymptomatic Grade 4 or symptomatic Grade 3A/B rejection is treated with anti-rejection drugs such as OKT3, daclizumab, basaliximab or high doses of methylprednisolone. For a patient who has persistent cell-mediated rejection that is unresponsive (i.e., refractory) to all attempts at treatment with the typical types and doses of drugs, extracorporeal photopheresis has been proposed and used as therapy (Patel, 2004).

Cardiac transplant rejection can result in significant morbidity and mortality. The increased doses of immunosuppressive drugs required to treat an episode of severe rejection substantially increase the risk of severe infections and malignancies (Dall'Amico, 1997). Recurrent episodes of rejection impact the patient's quality of life as well as graft survival (Guinti, 1999), which can ultimately lead to death if the patient is not retransplanted (Costanzo-Nordin, 1992).

2. Refractory Chronic Graft versus Host Disease (cGvHD)

Allogeneic hematopoietic cell transplantation (aHCT) is performed to treat and potentially cure a variety of malignant or non-malignant diseases. In an aHCT, cells are taken from the bone marrow or blood of a human donor and administered to a human host. Prior to transplantation, the host's bone marrow is destroyed with chemotherapy or radiation in order to eradicate the cancer cells and to prepare the host to accept the transplanted cells. After transplantation, immunosuppressive drugs are administered to the host to permit the new cells to implant without being destroyed by the host's immune system.

Unless the donor and host are identical twins, the genetic profile of the donor and of the host is similar but not identical. The degree of similarity between the two genetic profiles is an important factor in determining the risk of triggering immunologically-mediated complications after the transplantation. For any transplantation, it is critical to match the donor's genetic profile as much as possible to the host's genetic profile in order to minimize this risk.

Graft versus host disease (GvHD) is a complication of transplantation that can develop in the host. The complication occurs when the transplanted immune cells from the donor recognize the host's cells as foreign and therefore attack them. In other words, GvHD occurs due to the presence of immunologic mismatch between the donor's stem cells and the host's cells.

Graft versus host disease may have an acute or chronic onset. The clinical profile of each is distinct. The signs and symptoms of acute GvHD (aGvHD) typically start within a month of transplantation and include skin rash, diarrhea, and abnormal liver function tests. In addition to skin rash and abnormal liver function tests, the signs and symptoms of chronic GvHD (cGvHD) are more systemic and include dry eyes and mouth, hair loss, lung and gastrointestinal disorders. The severity of the clinical manifestations is denoted as mild, moderate, or severe. Severe or treatment-refractory cases can be life-threatening.

Chronic GvHD can arise in a progressive, quiescent, or de novo manner. In progressive cGvHD, the disease initially manifests as aGvHD, which doesn't resolve prior to the onset of the systemic signs and symptoms typically associated with cGvHD. With quiescent cGvHD, the patient's aGvHD is successfully treated prior to the onset of cGvHD. Patients with the de novo form of cGvHD do not have aGvHD at all.

Treatment of cGvHD consists of suppressing the immune response, but doing so without damaging the new marrow. High doses of corticosteroids or antibodies to T lymphocytes are administered to accomplish this goal. An alternative therapy does not currently exist if the disease does not respond to either of these treatments.

3. Bullous Pemphigoid and Pemphigus Vulgaris

Pemphigoid/Pemphigus is a group of autoimmune blistering diseases of the skin and/or mucous membranes. In an autoimmune disease, the body's immune system attacks its own organs or tissues by producing autoantibodies (antibodies against the self).

Our immune system produces antibodies that normally attack hostile viruses and bacteria in an effort to keep us healthy. In a person with pemphigus, however, the immune system mistakenly perceives the cells in skin and/or mucous membrane as foreign, and attacks them. Antibodies that attack one's own cells are called autoantibodies. The parts of the cells that are attacked in pemphigus are proteins called desmogleins. Desmogleins form the glue that attaches adjacent skin cells, keeping the skin intact.

When autoantibodies attack desmogleins, the cells become separated from each other. The skin virtually becomes unglued. This causes burn-like lesions or blisters that do not heal. In some cases, these blisters can cover a significant area of the skin

Treatment requires prescription drugs, many of which have side effects that often must be managed with other drugs. Additionally, these diseases can cause problems such as infection due to open wounds which may also require medication. The major modality of treatment is with immunosuppressive drugs, usually in combination with a corticosteroid. When an immunosuppressant is used with corticosteroids (steroid sparing), the dose of corticosteroid can often be reduced. Use of a steroid-sparing immunosuppressant, therefore, can help lower the undesirable side effects of prednisone.

Ultimately deaths in pemphigus and pemphigoid patients result more commonly from either complications of steroid therapy or unassociated diseases than the primary disease itself. In fact the severity and natural history of PV are variable, but before the advent of steroids, most patients with PV died as a result of this disease. Treatment with systemic steroids has reduced the mortality rate from the disease to 5-15%.

III. History of Medicare Coverage

In April 1998, CMS issued a national coverage determination for extracorporeal photopheresis providing coverage by Medicare only when used in the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) that has not responded to other therapy. CMS is not considering any change to this policy with respect to treatment of CTCL at this time.

On March 21, 2006, CMS received a formal request for reconsideration from the University of Pennsylvania Health System. The University requests that CMS update its NCD by allowing for the additional indications for extracorporeal photopheresis in treating the following specific disorders:

- refractory acute cardiac transplant rejection,
- refractory chronic graft versus host disease,
- pemphigus vulgaris, and
- bullous pemphigoid refractory to conventional immunosuppressive therapy.

In addition they request allowing Medicare contractor discretion for other conditions.

Benefit Category Determination
For an item or service to be covered by the Medicare program, it must meet one of the statutorily defined benefit categories outlined in the Social Security Act. Extracorporeal photopheresis, at a minimum, falls under the benefit category set forth in section 1861(s)(1) (physician services), a part B benefit.

IV. Timeline of Recent Activities

On March 21, 2006, CMS received a formal request for reconsideration from the University of Pennsylvania Health System.

On April 6, 2006 CMS opened a national coverage determination request to review the coverage of extracorporeal photopheresis. CMS requested public comment on whether there is adequate evidence, including clinical trials, for evaluating health outcomes of extracorporeal photopheresis for the requested indications in the Medicare population?

On October 4, 2006 CMS posted the proposed decision memorandum.

V. FDA Status

In 1999, The FDA approved UVADEX® (methoxsalen) Sterile Solution, which is indicated for extracorporeal administration with the UVAR Photopheresis System in the palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) that is unresponsive to other forms of treatment.

(http://www.fda.gov/cder/foi/label/1999/20969lbl.pdf)

VI. General Methodological Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that are used to evaluate the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum (see Appendix A).

VII. Evidence

A. Introduction

This section provides a summary of the evidence that CMS considered during the review. No randomized controlled clinical trials were found that investigated the use of extracorporeal photopheresis in patients with acute cardiac allograft rejection and cGvHD that is refractory to conventional immunosuppressive therapy. Additionally, there were no randomized controlled clinical trials found that investigated the use of extracorporeal photopheresis in pemphigus vulgaris or bullous pemphigoid. The evidence reviewed for this decision memorandum, therefore, consists of results from uncontrolled clinical trials and case studies that were published in a full length literature article.

B. Discussion of evidence

1. Questions

Is the evidence sufficient to conclude that extracorporeal photopheresis will have health benefits for the treatment of Medicare patients with acute cardiac allograft rejection that is refractory to standard immunosuppressive drugs?

Is the evidence sufficient to conclude that extracorporeal photopheresis will have health benefits for the treatment of Medicare patients with cGvHD that is refractory to standard immunosuppressive drugs?

Is the evidence sufficient to conclude that extracorporeal photopheresis will have health benefits for the treatment of Medicare patients with Bullous Pemphigoid and Pemphigus Vulgaris?

Outcomes:

1) Refractory Acute Cardiac Allograft Rejection

The goal of therapy is to eliminate the immunological attack on the heart. The primary outcome measured in the clinical studies and case studies that were reviewed for this decision memorandum was the change in the histology of serial endomyocardial biopsies. One clinical study also measured the change in the dose of the various drugs administered for immunosuppression. The EMB-focused outcome measures the impact of extracorporeal photopheresis on the severity of the immunological attack, which is a treatment effect. An outcome such as the change in immunosuppressive drug dose also measures a treatment effect.

None of the studies reviewed for this decision memorandum included health outcomes actually experienced by the patient, such as mortality or change in quality of life. However, an improvement in the rejection status with a concomitant reduction of immunosuppression drug doses can result in an improved clinical outcome if it leads to less risk of graft failure and infection (and cancer in the long term).

2) Refractory Chronic GvHD

The goal of therapy is to eliminate the immunological attack on the body. This attack can manifest in a variety of ways. For example, the main manifestation may be only cutaneous, or only pulmonary. Alternatively, a patient may experience the cutaneous, pulmonary, and hepatic manifestations of cGvHD. Accordingly, the assessment of the effects of treatment with extracorporeal photopheresis in patients with refractory cGvHD is dependent on the manifestations of the disease. The primary outcome measured in the clinical studies and case studies that were reviewed for this decision memorandum was the response rate. A positive response meant that there was a decrease in the activity of disease. The appearance (e.g., skin) or the function (e.g., blood liver function tests) of each part of the body involved by cGvHD was noted before and after treatment with extracorporeal photopheresis and then a response rate was calculated. The change in the dose of each immunosuppressive drug was also typically determined. A few of the studies also examined survival.

Survival is a health outcome actually experienced by the patient, which is the type of outcome that CMS prefers. Another health outcome is quality of life. It is possible that a positive response rate, especially regarding the cutaneous effects of cGvHD, which can significantly decrease a patient's quality of life, can result in an improved clinical outcome for the patient. Additionally, an improvement in disease activity due to extracorporeal photopheresis, even if it is less than a total resolution of disease activity, with a concomitant reduction of immunosuppression drug doses may result in an improved clinical outcome if it leads to less risk of infection. However, it is also possible that improved response rates, while improving quality of life, could also have negative effects on survival.

3) Bullous Pemphigoid and Pemphigus Vulgaris

The effects of treatment with photopheresis in patients with pemphigoid/pemphigus are assessed clinically for complete remission (absence of skin or mucous membrane lesions) or disease-free remission, a positive clinical response and decreased serum antibody levels. This is measured in relation to the type of drug/treatment and dosage.

2. External technology assessment

a. Refractory Acute Cardiac Allograft Rejection

For refractory acute cardiac allograft rejection, CMS did not commission an external technology assessment.

b. Refractory Chronic GvHD

CMS did not commission an external technology assessment for refractory cGvHD.

The BlueCross/BlueShield Association's TEC group performed a technology assessment (TA) titled "Extracorporeal Photophoresis for Graft-Versus-Host Disease" that was published in November, 2001. The objectives of the TA were to review the evidence for the use of extracorporeal photopheresis for patients with GvHD who were previously untreated, who were responding to established therapies, or who were refractory to established therapies. Only studies that reported outcomes on symptoms or disease activity were included.

The TA reviewed six studies of patients (cumulative sample size: 112) with refractory cGvHD, which the TEC group felt provided sufficient evidence to permit conclusions. All of the studies were uncontrolled. CMS reviewed only three of these six studies for this decision memorandum (Child, 1999; Smith, 1998; Besnier, 1997) because, of the remaining three studies, two were in abstract form only and one was a review.

In its review of the evidence, the TEC group found that the amount of benefit varied from study to study as well as by type of cGvHD. Two of six studies reported complete resolution of all disease activity plus discontinuation of immunosuppressive drug treatment for thirteen of 25 patients. Three studies reported significant symptomatic improvement in the majority of patients but no complete resolution of disease activity. The remaining study showed improvement of disease activity for half of the patients with de novo cGvHD but for only 25% of patients with progressive or quiescent cGvHD.

The TEC group concluded that the evidence demonstrates that extracorporeal photopheresis improves the net health outcome for patients with refractory cGvHD, and therefore extracorporeal photopheresis met their criteria when used to treat patients with cGvHD that is refractory to established therapy (Blue Cross/Blue Shield Association TEC, 2001).

c. Bullous Pemphigoid and Pemphigus Vulgaris

For bullous pemphigoid and pemphigus vulgaris, CMS did not commission an external technology assessment.

3. Internal technology assessment

a. Evidence Collection

1) Refractory Acute Cardiac Allograft Rejection

For refractory acute cardiac allograft rejection, CMS performed a literature search using PubMed to find clinical trials or meta-analyses evaluating the use of extracorporeal photopheresis in the treatment of patients with acute cardiac transplantation rejection refractory to standard immunosuppressive drugs. The search terms used were “graft rejection,” “heart transplantation,” and “photopheresis.” The search was limited to the English language and specific for the human population.

CMS also reviewed the information submitted by the NCD requestor. This evidence consisted of eleven published articles of which only one, a case study, reported health-related outcomes around the use of extracorporeal photopheresis to treat patients with acute cardiac transplantation rejection (Lehrer, 2001). Of the remaining ten articles, seven provided background information about cardiac transplantation, heart failure or immunosuppression. The other three articles, which provided either expert opinion about extracorporeal photopheresis or a clinical trial regarding the use of extracorporeal photopheresis to prevent acute cardiac allograft rejection, are presented in the Expert Opinion section of this decision memorandum.

2) Refractory Chronic GvHD

CMS performed a literature search using PubMed to find clinical trials or meta-analyses evaluating the use of extracorporeal photopheresis in the treatment of Medicare patients with cGvHD refractory to standard immunosuppressive drugs. The use of extracorporeal photopheresis for the treatment of aGvHD or for the prevention of cGvHD was not reviewed for this NCD. The search terms used were “graft vs. host disease,” or “graft vs. host reaction,” and “photopheresis.” The search was limited to the English language and specific for the human population.

CMS reviewed the information submitted by the NCD requestor. This evidence consisted of eight published articles of which four reported the health-related outcomes of a clinical trial about the use of extracorporeal photopheresis to treat patients with steroid-resistant or refractory cGvHD (Foss, 2005; Ilhan, 2004; Child, 1999; Greinix, 1998), of the remaining four articles; one presented a study that examined the immunologic mechanism of action of extracorporeal photopheresis. The other three articles are presented in the Expert Opinion section of this decision memorandum.

CMS also reviewed the information submitted in a public comment by Therakos, Inc. Of the nineteen published full length articles contained in the public comment that reported the health-related outcomes of a clinical trial or meta-analysis or case study in adult patients treated with extracorporeal photopheresis for cGvHD but were not already submitted by the requestor, seven were clinical trials (Garban, 2005; Couriel, 2005; Rubegni, 2005; Apisarnthanarax, 2003; Seaton, 2003; French, 2002; Smith, 1998) and one was a case study in patients with refractory cGvHD (Besnier, 1997).

Of the remaining eleven articles, eight provided background about cGvHD or the mechanism of action of extracorporeal photopheresis or information about the use of extracorporeal photopheresis in patients who did not have cGvHD. The other three articles are presented in the Expert Opinion section of this decision memorandum.

A Blue Cross/Blue Shield TEC technology assessment from 2001 was also submitted in the public comment. This technology assessment is presented in the External Technology Assessment section of this decision memorandum.

3) Bullous Pemphigoid and Pemphigus Vulgaris

CMS performed a literature search using PubMed to find any peer reviewed journal literature evaluating the use of extracorporeal photopheresis in the treatment of patients with PV or PB. The search terms used were ("Pemphigus"[MeSH Major Topic] OR "Pemphigoid, Bullous"[MeSH Major Topic] OR "Pemphigoid, Benign Mucous Membrane"[MeSH Major Topic]) AND ("Immunotherapy"[MeSH Major Topic] OR "Photopheresis"[MeSH Major Topic]).

CMS also reviewed the information submitted by the NCD requestor, and examined a TA by Blue Cross/Blue Shield. The resulting literature we reviewed including the submissions by the requesters is as follows:

Published full length articles that were not submitted by the requesters included one review article by Shih WY, Sami N and Razzaque AA (2005) and a TA (BC/BS 2006 update).

Articles submitted by the requesters included two single-case reports (Gollnick HPM et al. 1993, Liang G, Nahass G, Kerdel FA. 1992), one 4-case report (Rook AH et al. 1990), and a non-controlled trial of 7 patients (Wollina U, Lange D, Looks A. 1999).

b. Evidence Summary

1) Refractory Acute Cardiac Allograft Rejection

Clinical Trials

Five clinical trials evaluating the use of extracorporeal photopheresis in the treatment of patients with acute cardiac allograft rejection refractory to standard immunosuppressive drugs were identified.

Dall'Amico R, Montini G, Murer L, et al. Extracorporeal photochemotherapy after cardiac transplantation: a new therapeutic approach to allograft rejection. International Journal of Artificial Organs 2000;23:49-54

This was a prospective, uncontrolled study conducted in eleven patients with a history of two or more grade 3A-3B acute rejection episodes during the three months prior to extracorporeal photopheresis despite standard immunosuppression therapy regimen extracorporeal photopheresis was performed as 2 consecutive daily treatments each week for one month, then two treatments biweekly for two months, then two treatments monthly for three months using the UVAR system and 200 micrograms of 8-MOP administered ex vivo. The change in EMB histology was the measured health outcome. A grade of 0 or 1A was considered to represent complete resolution of rejection.

Five men and six women were in the study. The age range was 35 to 65 years. One patient died during the six-month treatment period due to hepatitis C infection (details not provided) and one patient dropped out due to a relapse of rejection that was unresponsive to extracorporeal photopheresis and high doses of steroids. For the nine patients who completed six months of extracorporeal photopheresis treatment, all episodes of rejections were reversed after a mean time of 14.2 days (range 7-32 days). The changes in the EMB results are shown in the following table.

Change in EMB Results (n= 11 patients)

Histological Grade	Pre-extracorporeal photopheresis (% of biopsies; n= 110 biopsies)	During extracorporeal photopheresis (% of biopsies; n= 78 biopsies)
Negative (Grade 0)	25	27
1A	21	45
1B	6	2
2	6	8
3A	29	17
3B	13	1

Six of nine patients experienced a rejection relapse during the sixty-month follow-up period after extracorporeal photopheresis. Of these, four episodes were reversed with the resumption of extracorporeal photopheresis (details not provided by the authors), one episode was reversed using high-dose steroids, and one episode was reversed with methotrexate after failure of extracorporeal photopheresis and high-dose steroids. During extracorporeal photopheresis there was one case of interstitial pneumonia and one case of symptomatic hypotension in a patient with pre-existing anemia and low body weight.

The authors stated that “despite the efficacy and safety reported…extracorporeal photopheresis cannot be recommended for the treatment of all rejection episodes. Most allograft rejections are easily reversed by an inexpensive course of IV steroids and rejection relapses are observed only in a limited number of cases.” Furthermore, the authors suggest extracorporeal photopheresis may be indicated “for the treatment of allograft rejection in patients needing a reduction in standard immunosuppression because of complications such as severe infections, nephrotoxicity, obesity, osteopenia…and in recipients with refractory and recurrent rejections.”

Giunti G, Schurfeld K, Maccherini M, et al. Photopheresis for recurrent acute rejection in cardiac transplantation. Transplantation Proceedings 1999;31:128-129

In Giunti, 1999 a prospective, uncontrolled trial with six patients with a history of recurrent acute rejection despite daily triple immunosuppressive therapy was conducted. Extracorporeal photopheresis using the UVAR system and 200 micrograms of 8-MOP administered ex vivo was performed on 2 consecutive days weekly for 1 month, then once weekly for 1 month, then biweekly for 2 months, and then monthly for 2 months. The change in EMB histology was the measured outcome.

All of the patients were men. The age range was 50 to 66 years. Moderate acute rejection episodes decreased from 0.4 to 0.07 rejections per month per patient ($p<0.02$). Further details regarding how this outcome was determined were not provided. The number of patients who experienced a response to extracorporeal photopheresis, and to what degree, was also not provided. Immunosuppressive drug doses were reduced in all patients during the extracorporeal photopheresis treatment period. Four of six patients remained on reduced doses of immunosuppressive drugs after discontinuation of extracorporeal photopheresis treatment while two of the six patients had a single episode of grade IIIA rejection over the three months after extracorporeal photopheresis was discontinued that necessitated an increase in immunosuppressive dose levels.

The authors observed that extracorporeal photopheresis for acute recurrent cardiac transplant rejection is “safe, efficient and free of major side effects” but also stated that the use of extracorporeal photopheresis in this patient population “is still largely unexplored.”

Dall’Amico R, Montini G, Murer L, et al. Benefits of Photopheresis in the treatment of heart transplant patients with multiple/refractory rejection. Transplantation Proceedings 1997;29:609-611

This was a prospective, uncontrolled study in 22 cardiac transplant patients with a history of 2 or more acute episodes of rejection refractory to standard therapy during the 3 months prior to study entry. The UVAR system was used. One hundred micrograms of 8-MOP were administered ex vivo. There were two extracorporeal photopheresis groups:

Group 1: 2 consecutive daily extracorporeal photopheresis treatments every 4 weeks for 6 months (twelve treatments total)

Group 2: 2 consecutive daily extracorporeal photopheresis treatments weekly for 1 month then every 2 weeks for 2 months, then monthly for 3 months (22 treatments total)

There were twelve patients in Group 1 and ten patients in Group 2. The outcome of interest was the change in EMB histology. A Grade of 0 or 1A was considered to represent complete resolution of rejection.

Fifteen men and seven women were in the study. The mean age was 49.8 years in Group 1 and 50.4 years in Group 2. Each group had 1 patient drop out of the study. In Group 1, the patient dropped out due to a lack of vascular access. In Group 2, a patient died due to hepatitis C infection; further details were not provided.

Nine of eleven patients in Group 1 had resolution of rejection while all nine patients in Group 2 had resolution. The mean time to resolution was 29.5 days in Group 1 and 13.8 days in Group 2.

The mean number of relapses of rejection per patient during 6 months of extracorporeal photopheresis was 1.36 in Group 1 and 0.8 in Group 2. The number of courses of steroid-based rejection therapy used to treat the relapse was seven in Group 1 and one in Group 2. The number of courses of methotrexate-based rejection therapy used to treat the relapse was one in Group 1 and one in Group 2.

One patient in Group 1 experienced a herpes zoster infection. One patient in Group 2 developed interstitial pneumonia, and one patient with pre-existing anemia and low body weight had symptomatic hypotension during an extracorporeal photopheresis procedure.

The authors highlighted that a higher frequency of treatment (as given in Group 2) was associated with a lower number of rejection relapses and hence a corresponding decrease in immunosuppressive drug therapy. They concluded that extracorporeal photopheresis “could be considered safe and efficacious treatment for patients with repeated rejection episodes,” that a more aggressive treatment protocol is advisable, and that “increased clinical experience is necessary to evaluate and individualize frequency of treatment.”

Dall’Amico R, Livi U, Milano A, et al. Extracorporeal photochemotherapy as adjuvant treatment of heart transplant recipients with recurrent rejection. Transplantation 1995;60:45-49

The authors performed a prospective, uncontrolled study in eight cardiac transplant patients with a history of multiple acute rejection episodes despite a routine immunosuppression regimen. The UVAR system was used. Two hundred micrograms of 8-MOP was administered ex-vivo. Extracorporeal photopheresis was performed on 2 consecutive days every 4 weeks for 6 months. The outcomes measured were change in EMB histology, and the change in the dose of each immunosuppressive drug.

Six men and two women were studied. The age range was 36-58 years. The fraction of EMB biopsies that did not show evidence of rejection increased from 13% to 41% after extracorporeal photopheresis. A steroid dose reduction of 44% was seen in 7 patients, a cyclosporine dose reduction of 21% occurred in 5 patients, and an azathioprine dose reduction of 29% was demonstrated in 3 patients.

The authors noted the small sample size of this study but concluded that extracorporeal photopheresis was a safe procedure that allowed for improved control of recurrent rejection, particularly by permitting for the reduction in doses of steroids.

Costanzo-Nordin MR, Hubbell EA, O'Sullivan EJ, et al. Successful treatment of heart transplant rejection with photopheresis. Transplantation 1992;53:808-815.

A prospective, uncontrolled study was conducted on seven patients with histological evidence of moderate cardiac transplantation rejection despite routine immunosuppressive regimen. The UVAR system was used. The oral formulation of 8-MOP was administered. The frequency and total duration of extracorporeal photopheresis treatments were not provided. The outcome measured was change in EMB histology. Efficacy based on EMB results was classified as ongoing rejection, resolving rejection, or absent rejection.

Three men and four women were studied. The age range was 19-64 years. The average duration of post-extracorporeal photopheresis follow-up was five months. The seven patients had a total of nine episodes of rejection; five episodes were treated with one extracorporeal photopheresis procedure and the remaining four episodes were treated with two procedures. Eight of the nine rejection episodes were successfully treated with extracorporeal photopheresis. Resolution of histological evidence of rejection was seen an average of 33 days after the administration of extracorporeal photopheresis. No adverse events occurred during extracorporeal photopheresis. There were no deaths during the study. Two infections occurred after extracorporeal photopheresis but the details were not provided.

The authors concluded that the results of their study demonstrate that extracorporeal photopheresis may "be effective" for the treatment of hemodynamically-stable patients with moderate acute cardiac transplant rejection. They noted the preliminary nature of this study and called for further studies to determine the full extent of usefulness of extracorporeal photopheresis and to determine the optimal number of treatments needed to sustain a response. The authors state that they have initiated a prospective, randomized open-label trial to study patients with moderate rejection.

Meta-analyses

No meta-analyses were identified.

Case Study

One case study was reviewed.

Lehrer MS, Rook AH, Tomaszewski JE, DeNofrio D. Successful reversal of severe refractory cardiac allograft rejection by Photopheresis. Journal of Heart and Lung Transplantation 2001;20:1233-1236

This case study presented the results of four patients treated with extracorporeal photopheresis. Each patient had acute heart transplant rejection (Grade III or IV) refractory to standard immunosuppression therapy and anti-rejection therapy. All but one of the four patients began to experience rejection within weeks of transplantation. The details of extracorporeal photopheresis administration were not provided.

The age range was 20 to 54 years. All patients tolerated the extracorporeal photopheresis well. The delivery of extracorporeal photopheresis resulted in a change of the rejection status to Grade 0 or I. Two of four patients experienced a sustained response to extracorporeal photopheresis (four months and six years after completion of extracorporeal photopheresis). The remaining two patients had rejection-related complications within one year of completing extracorporeal photopheresis that resulted in death.

The authors “strongly recommend” the addition of extracorporeal photopheresis as a possible treatment for refractory acute rejection. They also noted that larger clinical trials are needed to determine the best way to insert extracorporeal photopheresis into the treatment protocol for acute rejection.

2) Refractory Chronic GvHD

Clinical Trials

Eleven clinical trials evaluating the use of extracorporeal photopheresis in patients with refractory cGvHD were reviewed. All of the clinical trials were uncontrolled.

Foss FM, DiVenuti GM, Chin K, et al. Prospective study of extracorporeal photopheresis in steroid-refractory or steroid-resistant extensive chronic graft-versus-host disease: analysis of response and survival incorporating prognostic factors. Bone Marrow Transplantation 2005;35:1187-1193.

A prospective, uncontrolled, single center clinical trial was conducted on adult patients with steroid-resistant or refractory cGvHD. The UVAR system was used; 8-MOP was administered ex vivo. Sixteen patients received extracorporeal photopheresis on two consecutive days every two weeks (Group 1) and the remaining seven patients received extracorporeal photopheresis on two consecutive days every week (Group 2). Extracorporeal photopheresis was performed until either a response plateau of two or more months or progression was seen. Overall response rate, survival, and the change in the dose of immunosuppression drugs were the outcomes assessed.

Twenty five patients were studied; 23 of these patients were adults (sixteen men and seven women). The age range was eighteen to 59 years.

Extracorporeal photopheresis was performed for a median of nine months (range: three-24 months). The overall response rate was 64%. Twenty of 25 patients had improvement of cutaneous manifestations of cGvHD. Six of thirteen patients with oral mucosal involvement had healing of the ulcerations. Three of six patients with joint involvement had increased flexibility. One patient with lung disease had 50% improvement. One patient with gastro-intestinal involvement had resolution of diarrhea.

The median survival was 51 months (measured from day of transplantation). Median survival for responders was 55 months and for non-responders was 39 months (p= 0.3). A dose reduction or the complete discontinuation of immunosuppressive drug therapy was seen in 11 patients on steroids, in twelve patients on mycophenolate mofetil, and in five patients on tacrolimus.

Fifteen patients had serious adverse events that were determined not to be related to the extracorporeal photopheresis procedure. One patient discontinued extracorporeal photopheresis due to recurrence of the primary disease. Ten deaths were reported but the details were not provided except to note that those who died received a median of five extracorporeal photopheresis cycles and the survivors received a median of twelve (a “cycle” refers to the collection of the white blood cells by the UVAR system).

The authors concluded that the results suggest a trend toward a higher response rate for patients with the progressive form of cGvHD compared to the de novo form, and that there does not appear to be an association between extracorporeal photopheresis dose and clinical response.

Garban F, Drillat P, Makowski C, et al. Extracorporeal chemophototherapy for the treatment of graft-versus-host disease: hematologic consequences of short-term, intensive courses. Haematologica 2005;90:1096-1101.

Garban, et al. conducted a prospective, uncontrolled, single center clinical trial in patients with steroid-resistant cGvHD. A Spectra cell separator was used rather than the UVAR system; 8-MOP was administered ex vivo. Six courses of extracorporeal photopheresis were given during the first three weeks (induction regimen). If a complete response or no response was seen, then treatment was discontinued. If a partial response was seen, then one course was administered per week until a complete response was achieved (consolidation regimen). Clinical response was the outcome assessed. A complete response was defined as a total resolution of all manifestations of cGvHD and a discontinuation of all immunosuppression drugs. A complete response for cutaneous involvement occurred when there was 100% resolution of all skin lesions or the presence of fixed and pigmented lesions. A partial response for cutaneous involvement was defined as a fifty percent or greater improvement of the skin manifestations, or complete resolution but continuation of immunosuppression. A fifty percent or greater improvement in one involved organ was also declared to be a partial response (further details not provided).

Fifteen patients with cGvHD were studied. The age range was fourteen to 62 years. Twelve of fifteen patients experienced at least a partial response. Twelve patients had cutaneous involvement; all completely responded with most responses occurring in the first weeks of treatment. Skin and GI involvement resolved in parallel fashion. Improvement in liver function was transient. The three patients with bronchiolitis obliterans experienced stabilization of disease without the need for steroids. Four patients became totally free of immunosuppression for more than one year. The range of the duration of response was zero to 72 months.

Six patients died from relapse of their malignant disease. Four of fifteen patients developed thrombocytopenia but most of these patients did not receive a blood transfusion.

The authors concluded that extracorporeal photopheresis is effective treatment for patients with steroid-resistant cGvHD, especially the lung forms of cGvHD, and that the use of extracorporeal photopheresis can reduce the duration of immunosuppression therapy. The authors also stated that more study is needed to determine the most effective manner to administer extracorporeal photopheresis (i.e., frequency, intensity and duration of dose administration).

Couriel DR, Hosing C, Saliba R, et al. Extracorporeal photochemotherapy for the treatment of steroid resistant chronic GVHD. Blood Prepublished online on December 20, 2005.

The authors performed a single-center retrospective chart review for all patients regardless of age with steroid-refractory cGvHD who were treated with extracorporeal photopheresis between January, 1998 and October, 2002. The UVAR system was used; 8-MOP was administered ex vivo. Extracorporeal photopheresis was performed two to four times per week until a partial response was observed; then the number of treatments was decreased by one per week. A maintenance schedule then consisted of two treatments every two weeks. The need for treatment discontinuation, the amount of titration, and the duration of treatment was determined by each patient's treating physician. Response to therapy (complete, partial, mixed or no response), the non-relapse mortality rate, and overall survival were assessed.

Seventy-one patients were included in the study (33 men and 38 women). The age range was five to 70 years (median age of 39 years). Neither the number of children nor the number of patients 65 years old or greater was reported.

The overall response rate was 61%. There were 43 patients who initially responded to treatment (fourteen complete responses and 29 partial responses). The median time from the onset of extracorporeal photopheresis to achieving a complete response was 27 days (range of thirteen to 238 days). Thirty of 43 patients maintained the initial response for a median duration of 18 months (range of 0.4-65 months); the remaining thirteen progressed after a median of 23 days (range of sixteen to 188 days).

Overall survival at 5 years was nineteen percent. The non-relapse mortality rate at five years was 46%. Causes of death included GvHD plus infection in 67% of deaths, relapse of primary disease in 29%, infection outside the setting of cGvHD or its treatment in two percent, and hemorrhage in two percent.

Four patients experienced mild, reversible toxicity that did not require discontinuing extracorporeal photopheresis (abdominal pain in one patient, hypertension in one patient, hypotension in one patient, and fever in one patient).

The authors concluded that their results demonstrated the “objective activity” of extracorporeal photopheresis in patients with steroid-resistant cGvHD and that the patients who responded had significantly lower non-relapse mortality. They also noted that extracorporeal photopheresis was “overall well tolerated, with no fatal toxicities.”

Rubegni P, Cuccia A, Sbano P, et al. Role of extracorporeal photochemotherapy in patients with refractory chronic graft-versus-host disease. British Journal of Haematology 2005;130:271-275.

Rubegni, 2005 presented the results of a prospective, uncontrolled, single center clinical trial in patients with steroid-refractory cGvHD. The UVAR system was used; 8-MOP administered ex vivo. The frequency of extracorporeal photopheresis administration was not stated.

An overall outcome score was calculated in an attempt to assess the role of extracorporeal photopheresis in the context of concomitant therapies for cGvHD. The following categories were used when considering the contribution of extracorporeal photopheresis:

- Determinant complete response seen in all involved organs plus a fifty percent or greater reduction in immunosuppression use
- Good status assigned if outcome is between determinant and ineffective
- Ineffective disease progression seen in an organ, or there was a need to increase immunosuppression, or complete response not seen in any organ plus immunosuppression was not reduced by fifty percent or greater

An overall outcome of Determinant or Good was given a score of one and classified as a response; an overall outcome of Ineffective was given a score of zero and classified as a non -response.

Thirty-two patients were studied (twenty men and twelve women). The age range was eighteen to 60 years.

Seventy-eight percent of the patients were responders (22% Determinant, 56% Good); 22% of patients were non-responders. Minor side effects such as hypotension, and venipuncture site hematomas were noted.

The authors concluded that overall extracorporeal photopheresis is a beneficial treatment for patients with steroid-refractory cGvHD. Extracorporeal photopheresis was particularly effective for patients with thrombocytopenia but less effective for patients with the lung forms of disease.

Ilhan O, Arat M, Arslan O, et al. Extracorporeal photoimmunotherapy for the treatment of steroid refractory progressive graft-versus-host disease. Transfusion and Apheresis Science 2004;30:185-187.

Ilhan et al. reported the uncontrolled results of eight patients with steroid-refractory cGvHD who received extracorporeal photopheresis using the UVAR system and 8-MOP administered ex vivo. Extracorporeal photopheresis was performed over two consecutive days every four weeks until the signs and symptoms of GvHD resolved (up to eight months maximum). The outcomes measured were response to therapy for each involved organ, and change in dose of immunosuppression drugs.

Two men and six women were included in the report. The age range was seventeen to 45 years. Six of the eight patients had a favorable response (e.g., improvement in respiratory function, complete resolution of cutaneous and oral mucosal lesions, or regression of cholestatic parameters). One patient experienced Grade 4 thrombocytopenia.

The authors concluded that extracorporeal photopheresis can be beneficial, especially for patients with cutaneous and mucosal involvement. The beneficial effect is less consistent for patients with systemic disease.

Apisarnthanarax N, Donato M, Korbling M, et al. Extracorporeal photopheresis therapy in the management of steroid-refractory or steroid-dependent cutaneous chronic graft-versus-host disease after allogeneic stem cell transplantation: feasibility and results. Bone Marrow Transplantation 2003;31:459-465.

Apisarnthanarax et al. performed a single-center retrospective chart review on patients with steroid-refractory or dependent cGvHD who were treated with at least 4 weeks of extracorporeal photopheresis between September, 1998 and August, 2001. The UVAR or UVAR XTS system was used; 8-MOP was administered ex vivo. Extracorporeal photopheresis was performed using a variety of schedules and intensity depending on disease severity over the 36 month study period. The response to therapy was assessed as complete, partial, or steroid-sparing. Overall and cGvHD-related mortality rates were also determined.

Thirty-two patients were studied; thirty of these patients were adults. The men to women ratio was 1:1.3. The age range was five to 70 years. Thirty-four percent of patients had steroid-refractory disease and 66% had steroid-dependent disease.

The median number of extracorporeal photopheresis sessions was six per month and the median number of total sessions was 34. Extracorporeal photopheresis sessions were discontinued due to a lack of response or a response plateau in ten patients, a resolution of disease in five patients, death due to cGvHD progression or infection in five patients, intravenous access difficulty in one patient, central line infection in one patient, fluid overload in one patient, and deep vein thrombosis in one patient.

The overall response rate was 56%. The complete response rate was 22%. Responders received a median of six sessions and nonresponders received a median of seven sessions per month. Eighteen of 28 (64%) patients initially on steroids had a fifty percent reduction in dose; six of eighteen patients eventually discontinued all steroid use.

Three patients had complications related to the indwelling catheter that was used to administer the extracorporeal photopheresis treatments. Minor treatment-related side effects such as transient hypotension were noted but not quantified.

The authors concluded that the study results suggest that extracorporeal photopheresis is “a safe and effective adjunctive therapy for steroid-refractory cGvHD.” They also stated that more research is needed to determine the best way to administer extracorporeal photopheresis as well as the long-term efficacy of extracorporeal photopheresis.

Seaton ED, Szydio RM, Kanfer E, et al. Influence of extracorporeal photopheresis on clinical and laboratory parameters in chronic graft-versus-host disease and analysis of predictors of response. Blood 2003;102:1217-1223.

This prospective, uncontrolled, single center clinical trial studied 28 patients with steroid-refractory cGvHD. The UVAR or UVAR XTS system was used; 8-MOP was administered either IV or ex vivo. Extracorporeal photopheresis was initially performed on two consecutive days every two weeks for four months and then monthly. At six months a decision was made to either halt or continue treatment depending on the clinical response and patient preference. The outcome measured was response to therapy (for each organ of involvement). A standard quantitative measurement of extent of disease was used for each organ system. A clinical response was defined as a 25% or greater change from baseline plus stable or reduced doses of immunosuppression.

Twenty men and eight women were studied. The age range was eighteen to 51 years. The median duration of treatment was six months (range 1 – 58 months). Of the 21 patients with cutaneous disease, eight were responders at three months and ten were responders at six months. A complete remission was seen in one patient. For 25 patients with hepatic disease, seven were responders at three months. Eight patients with pulmonary disease experienced a two percent reduction in vital capacity. Pre-treatment immunosuppression doses remained stable in fifteen of 28 patients, were reduced in nine of 28, and were increased in four of 28 patients.

Five patients had severe complications: four deaths due to advanced cGvHD, and one case of acute respiratory distress syndrome that fully resolved.

The authors concluded that extracorporeal photopheresis has a beneficial effect and a low toxicity profile when used in patients with steroid-dependent or steroid-resistant cGvHD, which indicates that extracorporeal photopheresis may be of use as adjunctive therapy. The authors highlighted the clinical benefit of the steroid-sparing effects of extracorporeal photopheresis and acknowledged the persistent high cGvHD-related mortality rate in this patient population.

French LE, Alcindor T, Shapiro M, et al. Identification of amplified clonal T cell populations in the blood of patients with chronic graft-versus-host disease: positive correlation with response to photopheresis. Bone Marrow Transplantation 2002;30:509 -515.

French, et al. conducted a retrospective, uncontrolled, single center clinical study of twelve patients with cGvHD. The UVAR system was used; 8-MOP was administered orally. Extracorporeal photopheresis was performed on two consecutive days once a month but the total duration of treatment was not stated. Response to therapy (complete response, partial response, or no change) for each organ involved was the outcome measured.

Seven men and five women were studied. The age range was 25-59 years. Nine of the twelve patients had a decrease in the dose of at least one immunosuppressive drug. A cutaneous response was seen in eight of twelve patients (with two complete responses). A musculoskeletal response was seen in five of six patients (with one complete response). An oral/mucosal response was seen in all five patients with oral/mucosal involvement (with no complete responses). All two patients with hepatic involvement had a response to therapy with one having a complete response.

The authors concluded that extracorporeal photopheresis is effective in patients with steroid-refractory cGvHD. Due to the inability to find baseline parameters that predict response to treatment, “patient selection must continue to be made on clinical grounds.” The authors also noted that “extracorporeal photopheresis is a time-consuming and relatively expensive treatment that requires specialized equipment and staff expertise.”

Child FJ, Ratnavel R, Watkins P, et al. Extracorporeal photopheresis (ECP) in the treatment of chronic graft-versus-host disease (GVHD). Bone Marrow Transplantation 1999;23:881-887.

Child et al. reported the uncontrolled results of nine men and two women with refractory cGvHD who received extracorporeal photopheresis using the UVAR system and 8-MOP administered ex vivo. All patients had cutaneous involvement. Extracorporeal photopheresis was performed twice a month for four months, and then once a month for three months. Response to therapy for each involved organ was measured.

The age range of the patients studied was eighteen to 47 years. There were three drop-outs from the study: one patient died from cyclosporine-induced renal failure, one patient experienced pneumonia that was successfully treated (with subsequent restart of extracorporeal photopheresis), and one patient withdrew from the study by request after four months of treatment.

The authors reported that the results for ten patients were included in the analysis. All ten patients with cutaneous involvement had a response to treatment (but no complete response was seen), two of four patients with oral/mucosal involvement had a response (no complete responses), one of six with hepatic involvement had a response (no complete responses), and two of five with pulmonary involvement had a response (no complete responses). In the majority of patients the improvement in skin disease was greater during the first four months of treatment than during the next three months. The greater response corresponds to the greater dose of extracorporeal photopheresis received during the first four months. All patients were able to reduce the dose of immunosuppressive drugs. There were no significant side effects.

The authors concluded that extracorporeal photopheresis is safe and effective as adjunctive treatment for cutaneous or systemic disease in patients with steroid-resistant cGvHD.

Greinix HT, Volc-Platzer B, Rabitsch W, et al. Successful use of extracorporeal photochemotherapy in the treatment of severe acute and chronic graft-versus-host disease. Blood 1998;92:3098-3104.

The article by Greinix et al. reports on the uncontrolled results of fifteen consecutive patients with refractory cGvHD that were treated with extracorporeal photopheresis using the UVAR system and 8-MOP administered ex vivo. Extracorporeal photopheresis was performed on two consecutive days every two weeks for three months and then every four weeks until there was resolution of sign and symptoms of cGvHD. The outcomes measured were response to therapy for each involved organ (complete response, partial response, no change, or no response), and survival.

All fifteen patients with cutaneous involvement had a response (twelve with a complete response). All four patients with musculoskeletal involvement had a response (no complete responses). All eleven patients with oral/mucosal involvement had a complete response. For ten patients with hepatic involvement, nine had a response (seven with a complete response). Five of six patients with ocular involvement had a response (one complete response). Two of three patients with thrombocytopenia had a response (two complete responses). Fourteen patients were alive after a median follow-up of fifteen months; the one death was due to a relapse of the primary disease.

The authors concluded that extracorporeal photopheresis has “some efficacy in the treatment of drug-resistant chronic GvHD, with minor overall toxicity.”

Smith EP, Sniecinski I, Dagis AC, et al. Extracorporeal photochemotherapy for treatment of drug-resistant graft-versus-host disease. Biology of Blood and Marrow Transplantation 1998;4:27-37.

This was a prospective, uncontrolled, single center, clinical study in patients with refractory cGvHD who were given extracorporeal photopheresis using the UVAR system. 8-MOP was administered orally and the dose was adjusted based on serum levels. Extracorporeal photopheresis was performed on two consecutive days every three weeks and then two to three times per week. The frequency of treatment was then modified on an individual basis. While the main goal was to study the characteristics of the T lymphocytes both before and after extracorporeal photopheresis, a response to therapy for each involved organ was measured as complete response, partial response, or no response.

Eighteen patients were studied. The sex and age profiles of the patients were not provided. Three patients had a complete response, three had a partial response, two had an initial response with ultimate progression of disease, and ten had no response to treatment. There were eleven deaths related to either GvHD progression, a relapse of the primary disease, and/or infection. Toxicities included GI upset, catheter-related complications (in five patients) including sepsis (in four patients), and an increased need for red blood cell and platelet transfusions (in one patient).

The authors acknowledged the preliminary nature of the results but concluded that extracorporeal photopheresis is an effective treatment for cGvHD.

Meta-analyses

No meta-analyses were identified.

Case Study

One case study was reviewed.

***Besnier DP, Chabannes D, Mahe B, et al. Treatment of graft-versus-host disease by extracorporeal photochemotherapy. Transplantation 1997;64:49-54*.**

Besnier et al. reported the uncontrolled results of five (but only three were adults) patients with steroid-refractory or intolerant cGvHD who received extracorporeal photopheresis using a Spectra cell separator (rather than the UVAR system) and 8-MOP administered ex vivo. Extracorporeal photopheresis was performed three times per week for three weeks and then the frequency of administration was tapered as clinically indicated. The outcomes measured were response to therapy for each involved organ, and the need for immunosuppression.

A 42 year old patient had initial improvement without the need for immunosuppressive drugs but then experienced a relapse of cutaneous signs and symptoms seven months after discontinuing treatment with extracorporeal photopheresis.

A 39 year old patient had significant improvement of muscular cGvHD after three weeks of extracorporeal photopheresis along with a decrease in the immunosuppressive drug regimen. By three months the patient had regained normal strength and all immunosuppression drugs were stopped. The patient is clinically stable at one year.

A 26 year old patient with bronchiolitis obliterans of sufficient severity to necessitate placement on the wait list for a lung transplant had a slight decrease in the steroid dose after extracorporeal photopheresis treatments. The patient is clinically stable after six months but is still awaiting transplantation.

The authors concluded that extracorporeal photopheresis “may be helpful for the treatment of severe cGvHD and the avoidance of increased immunosuppression.”

3) Bullous Pemphigoid and Pemphigus Vulgaris

With respect to the NCD request for CMS to cover extracorporeal photopheresis for the indication of pemphigus vulgaris (PV) or bullous pemphigoid (BP) we provide the following review of literature submitted by requesters and found by CMS’s literature search. These references presented data that supported extracorporeal photopheresis use in the treatment of BP and PV.

Clinical Trials

Wollina et al. reported a 7- person no control group trial having 4 females 3 three males, with three different autoimmune types of bullous disease (PV, BP, and pemphigus folieaceus) (Wollina et al. 1999). Pemphigus foliaceous is defined as chronic pemphigus in which extensive scaling dermatitis, with no perceptible blistering, may be present in addition to the bullae. With varying follow-up times ranging from 4 -42 months, they reported partial or complete remission secondary to extracorporeal photopheresis treatment with varying numbers of treatment cycles. Complete remission was defined as elimination of all cutaneous and mucous membrane blisters and erosions, while partial remission was indicated to be improvement but not complete elimination of those lesions. Details on these patients are listed in the following table.

Clinical characteristics and outcome in patients with pemphigus or BP treated with adjuvant extracorporeal photopheresis								
Patient		Sex	Diagnosis		Drugs		Response	

Clinical characteristics and outcome in patients with pemphigus or BP treated with adjuvant extracorporeal photopheresis

	Age (yrs)			Disease Duration (months)		extracorporeal photopheresis Cycles		Follow-up (months)
1	44	M	PV	12	100mg pred	2	CR	24
2	48	M	PF	36	15mg pre/150 mg aza	8	PR	33
3	85	F	BP	5	100mg pred	1	CR	32
4	83	F	BP	24	100mg pred	4	CR	42
5	44	F	PV	2	200mg pred	2	CR	34
6	70	M	BP	3	200mg pred/150 mg aza	2	CR	4
7	31	F	PV	3	100mg pred	3	CR	10

PF = Pemphigus Foliaceous; pred = prednisolone; aza = azathiaprine; CR=complete remission; PR=partial remission

Meta-analyses

None

Case Study

Three references were submitted. Two of these were single case reports and a third referred to 4 case reports while describing two of them. In a case report by Gollnick et al. his German group treated a 37 year old woman with a refractory case of PV and believed they had a successful result (Gollnick et al., 1993) defined by near complete remission. Liang et al., in Miami, treated a 31 year old man who they reported had successful treatment with extracorporeal photopheresis for body lesions covering 70% of his body due to PV (Liang et al., 1992) with near complete resolution of the lesions and remission. Rook et al. reported 4 cases of PV in total, with varying degrees of partial success as measured by near or complete remission at varying follow-up times (Rook et al., 1990).

We found one additional reference in the literature. Shih et al. wrote a review in which the authors reported that in 6 studies reviewed regarding PV treatment via extracorporeal photopheresis, a total of thirteen patients with PV, an average of two per study, were presented (Shih et al. 2005). However, there were no control groups in these very small studies. The review article states “extracorporeal photopheresis may be an effective alternative therapy in the treatment of PV. However, the number of patients studied has been too small to make any recommendations.” Also three of the six reports included repetition of data described above.

4. Medicare Coverage Advisory Committee (MCAC) Meeting

Not applicable.

5. Evidence-based guidelines

No evidence-based guidelines were identified for the use of extracorporeal photopheresis for refractory acute cardiac allograft rejection, refractory cGvHD, or bullous pemphigoid and pemphigus vulgaris.

6. Professional Society Position Statements

None found.

7. Expert Opinion

For refractory acute cardiac allograft rejection, the NCD requestor submitted three published articles that were noted but not evaluated by CMS because they do not report the results of a clinical trial meta-analysis or case study that examined a health-related outcome in adult patients with refractory acute cardiac allograft rejection who were treated with extracorporeal photopheresis. In Dall'Amico, 2002 the authors reviewed the past and current use of extracorporeal photopheresis in patients who have received a transplantation (cardiac or non-cardiac) and noted that extracorporeal photopheresis is effective with a "histological resolution of acute rejection…reported in 89% of cardiac transplant patients" without the typical drug-based immunosuppressive complications. It was also noted that the best way to administer extracorporeal photopheresis is still to be determined. In an editorial about the use of extracorporeal photopheresis for the prevention of cardiac allograft rejection (Barr, 2003), the difficulties with using drug-based immunosuppression as well as the clinical history of extracorporeal photopheresis use were presented. The author stated that "present and future studies will help to define the role of this novel, safe, and non-toxic, immunomodulating technology in the field of transplantation." In a clinical trial about the use of extracorporeal photopheresis to prevent acute cardiac allograft rejection (Barr, 1998), the authors found that adding extracorporeal photopheresis to a standard immunosuppressive drug regimen decreased the risk of the onset of acute rejection without increasing the incidence of infection.

For refractory cGvHD, the NCD requestor submitted three articles that were noted but not evaluated by CMS because they do not report the results of a clinical trial or meta-analysis or case study that examined a health-related outcome in adults. In Foss, 2003 the authors reviewed the mechanism of action and clinical efficacy of extracorporeal photopheresis for patients with cGvHD and noted that extracorporeal photopheresis has been shown to be an effective therapy for patients with cGvHD. Dall'Amico et al. (2002) reviewed clinical studies of extracorporeal photopheresis conducted in patients with refractory cGvHD. They concluded that extracorporeal photopheresis should be considered as a second-line therapy for patients with refractory cGvHD, and that randomized clinical trials are needed to confirm the efficacy of extracorporeal photopheresis. In Coyle, 2004 the results of a clinical trial of extracorporeal photopheresis in pediatric patients with cGvHD were briefly presented. The authors concluded that extracorporeal photopheresis improves the cutaneous manifestations of cGvHD and decreases drug immunosuppression use in a subset of patients.

Therakos, Inc. submitted two review articles about extracorporeal photopheresis (Komanduri, 2006; Sniecinski, 2000) and one article that presented the results of a clinical trial in pediatric patients with cGvHD (Dall'Amico, 1997). Komanduri et al. reviewed the available clinical and non-clinical studies of extracorporeal photopheresis in GvHD and noted that prospective randomized clinical trials "may be required to clearly establish the role of extracorporeal photopheresis." In Sniecinski, 2000 the authors reviewed the role of extracorporeal photopheresis in the treatment of patients with cGvHD and concluded that extracorporeal photopheresis ideally should be used before second-line immunosuppressive drugs, which can mask the immunomodulatory effects of extracorporeal photopheresis. They also called for randomized clinical trials that study the efficacy of the early use of extracorporeal photopheresis. Dall'Amico et al. (1997) studied pediatric patients with refractory cGvHD and concluded that extracorporeal photopheresis is a "non-aggressive" treatment that may benefit some patients with refractory cGvHD.

8. Public Comment

30-day Initial Public Comment Period

During the initial 30-day public comment period, CMS received comments from twenty-one individuals and organizations. All commenters advocate for the expansion of CMS' current policy of extracorporeal photopheresis for cGvHD.

30-day Final Public Comment Period

During the final 30-day public comment period, CMS received comments from forty-three individuals and organizations. All commenters advocate for the expansion of CMS' current policy of extracorporeal photopheresis.

<u>Comments from Universities/Medical Centers</u>

CMS received twenty-one public comments from Universities/Medical centers. Seven commenters support CMS's decision to cover patients with acute cardiac allograft rejection whose disease is refractory to standard immunosuppressive drug treatment; and patients with chronic graft versus host disease whose disease is refractory to standard immunosuppressive drug treatment. Eleven commenters support specifically covering cGvHD. One commenter did not mention any indications, but was in support of the decision and two comments were not relevant to the coverage decision.

Some of the commenters that were in support of our coverage decision also suggested broadening the coverage decision. One commenter was disappointed that we did not support the use of photopheresis for the treatment of scleroderma and pemphigus vulgaris. In response, scleroderma is out of the scope of this national coverage determination reconsideration request. CMS has determined that there is insufficient evidence to conclude that extracorporeal photopheresis treatment for pemphigus vulgaris will improve health outcomes for Medicare patients in general without limitations. Another commenter suggests that CMS should cover photopheresis for lung transplant patients. In response, lung transplantation is out of the scope of this national coverage determination reconsideration request.

Comments from Hospitals/Clinics

CMS received twenty public comments from Hospitals/ Clinics and Physicians. Three commenters support CMS's decision to cover patients with acute cardiac allograft rejection whose disease is refractory to standard immunosuppressive drug treatment; and patients with chronic graft versus host disease whose disease is refractory to standard immunosuppressive drug treatment. Fifteen commenters support specifically covering cGvHD. Two commenters did not mention any indications, but were in support of the decision and one comment was not relevant to the decision.

Some of the commenters that were in support of our coverage decision also suggested broadening the coverage decision. One commenter suggests that CMS should look at lung transplant rejection. In response, lung transplantation is out of the scope of this national coverage determination reconsideration request. Another commenter suggests that CMS cover ECP in select patients with acute GvHD. This commenter stated that she attached articles to the public comment regarding acute GvHD. CMS did not receive the attached articles and contacted the requestor twice but did not receive the articles. However, acute GvHD is out of the scope of this national coverage determination reconsideration request.

Comments from General Public

CMS received one comment from someone who did not identify themselves. The comment was in favor of the proposed decision.

Comments from Professional Societies

CMS received a comment form the American College of Cardiology (ACC). While ACC was in support of the coverage decision, they point out that although it does not affect the coverage decision, a new grading system for endomyocardial biopsies has been published and adopted to replace the classification developed by Billingham et al. which was cited in the proposed decision memorandum. In response, CMS is aware of the new grading system; however, because the new grading system does not affect how we reviewed and interpreted the evidence regarding photopheresis, we will continue to use the Billingham classification.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be “reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member” § 1862(a)(1)(A).

In analyzing the evidence, CMS asked is the evidence sufficient to conclude that extracorporeal photopheresis will have health benefits for the treatment of Medicare patients with:

- acute cardiac allograft rejection that is refractory to standard doses of immunosuppressive drugs,
- cGvHD that is refractory to standard doses of standard immunosuppressive drugs, and
- bullous pemphigoid and pemphigus vulgaris?

The evidence available to support the use of extracorporeal photopheresis in patients with these severe immunological disorders comes from small uncontrolled clinical trials and case studies. The studies of bullous pemphigoid and pemphigus vulgaris were exclusively very small case studies. A controlled clinical trial is the preferred trial design because it provides standardized treatment regimen (e.g., the frequency, intensity, and duration of extracorporeal photopheresis administration) and assessment methods, and a comparison group. These features are designed to prevent the introduction of bias and the confounding of the data.

The vast majority of patients studied were not of Medicare age (i.e., 65 years of age or older) however this is less of a concern with post-transplantation patients because Medicare provides for the pre-operative and post-operative care for patients in the Medicare program who have received a heart or allogeneic hematopoietic cell transplantation regardless of age.

CMS considered the requestors suggestion that local Medicare contractors be permitted discretion to cover other conditions such as pemphigus foliaceous, acute graft versus host disease, systemic sclerosis and rejection of other transplanted solid organs, but found insufficient evidence to warrant proposing contractor discretion.

1) Refractory Acute Cardiac Allograft Rejection

The evidence available to support the use of extracorporeal photopheresis in patients with refractory acute cardiac allograft rejection comes from five prospective clinical trials and from a case study. The fifth clinical trial (Dall'Amico, 1997) included a modicum of control by having two groups of patients with each group receiving a different cumulative dose of extracorporeal photopheresis. The remaining four clinical trials were uncontrolled, which may have impacted the quality of the results generated by these trials by potentially introducing significant bias and confounding the data. All five clinical trials as well as the case study were small in sample size. The various extracorporeal photopheresis treatment protocols used (e.g., frequency and duration of extracorporeal photopheresis administration, 8-MOP formulation) throughout the studies is an additional design issue that prevents pooling of the evidence in an attempt to overcome the small sample size of each study.

Notwithstanding the study design concerns, the results from the clinical studies do show a benefit to performing extracorporeal photopheresis in patients with refractory acute cardiac allograft rejection. In Dall'Amico, 1997, the authors reported a greater than 80% response rate within one month of initiating extracorporeal photopheresis. A dose-response relationship was also exhibited where the group that received more extracorporeal photopheresis treatments had a higher response rate and a shorter time to response.. The duration of response was not stated. In an article published in 2000, Dall'Amico et al. noted a 100% response rate. In Dall'Amico, 1995 the need for reduced doses of immunosuppressive drugs was shown.

While the evidence suggests that there is a short term benefit of extracorporeal photopheresis, the long term benefits have not been demonstrated in this patient population. In fact, while the patients in Dall'Amico, 2000 experienced a 100% response rate to extracorporeal photopheresis, there was also a 67% rate of relapse of disease after extracorporeal photopheresis was discontinued. The remaining studies apparently did not study, or at least report, the long term effects of extracorporeal photopheresis. Hence, questions remain regarding the most appropriate way to administer extracorporeal photopheresis to patients with refractory acute cardiac allograft rejection.

A safety problem was not demonstrated in any of the studies beyond the known complications associated with the extracorporeal photopheresis procedure (e.g., transient hypotension). In Dall'Amico, 1997 the patients who received 22 extracorporeal photopheresis treatments did not appear to experience greater toxicity than the patients who received twelve treatments. In Dall'Amico, 2000, the patients were followed for 60 months after discontinuation of extracorporeal photopheresis treatments without any mention of extracorporeal photopheresis-related toxicity. However, attempts to associate side effects or complications with extracorporeal photopheresis are confounded by the concurrent use of immunosuppressive drugs, by the general clinical status of the patient, and in general by the lack of a control group for comparison.

Acute cardiac allograft rejection that has not responded to multiple attempts with multiple immunosuppressive drugs is a life-threatening disease that affects a small number of patients. Despite limitations in the evidence, the studies evaluated in this decision memorandum demonstrate that extracorporeal photopheresis improves some health outcomes for patients without an obvious sign of significant toxicity in patients with a disease process that has no alternative treatment. Therefore, CMS believes that the evidence is sufficient to conclude that extracorporeal photopheresis will have health benefits for the treatment of Medicare patients with acute cardiac allograft rejection that is refractory to standard immunosuppressive drugs. Based upon the above findings, extracorporeal photopheresis is reasonable and necessary for patients of any age with acute cardiac allograft rejection whose disease is refractory to standard immunosuppressive drug treatment.

2) Refractory Chronic GvHD

The evidence to support the use of extracorporeal photopheresis in patients with cGvHD that is refractory to standard immunosuppressive drugs was derived from eleven clinical trials, five of which were prospective, and one case study. All of the trials were uncontrolled trials so there is an increased risk of assessment bias and data confounding. The small sample size of each trial (with the exception of Couriel, 2005) may have also impacted the overall quality of the evidence, especially given the highly variable extracorporeal photopheresis treatment protocol used in each trial.

Despite the identified study design limitations, the evidence demonstrates some benefit of extracorporeal photopheresis in this patient population. Foss et al. reported a clinical response rate of 64% while Couriel et al. reported a 61% clinical response rate and Rubegni et al. noted a 78% response rate. The benefits, however, vary by organ of involvement. The most prominent and consistently reported improvement is for the cutaneous manifestations of cGvHD (Foss, 2005; Ilhan, 2004; French, 2002; Child, 1999; Greinix, 1998). The oral/mucosal manifestations also improve with extracorporeal photopheresis treatment (Ilhan, 2004; French, 2002; Greinix, 1998). Improvement of the systemic manifestations of cGvHD (e.g., liver or lung function), however, was not clear from the evidence (Seaton, 2003). There is also some evidence that extracorporeal photopheresis leads to decreased doses of immunosuppressive drugs (Apisarnthanarax, 2003; French, 2002).

Relapse of cGvHD was not widely reported. However, it is not possible to evaluate the durability of the benefits of extracorporeal photopheresis due to the short duration of follow-up and the highly variable extracorporeal photopheresis administration schedule used in each clinical trial. For example, in Couriel, 2005, after the administration of a standard extracorporeal photopheresis regimen each patient's physician was permitted to decide both the need for continuation of extracorporeal photopheresis treatment and the treatment frequency.

An obvious safety concern during the actual extracorporeal photopheresis procedure is not evident from the evidence. Patient mortality, as noted in the Seaton, 2003 and Smith, 1998 studies, is still a significant issue. However, since cGvHD is a life-threatening disease, it is not possible to discern if the high mortality is due to the disease (including the multiple toxic immunosuppressive drugs that the patient is taking) or due to extracorporeal photopheresis. In addition, the small sample size and the lack of a control group for comparison in each study prevent a determination of whether the death is due to inevitable disease progression or due to extracorporeal photopheresis.

Chronic GvHD that has not responded to multiple attempts with multiple immunosuppressive drugs is a life-threatening disease with a lack of alternative treatments that occurs in a small number of patients. Despite limitations in the evidence, it demonstrates some improved health outcomes for patients treated with extracorporeal photopheresis, particularly for the cutaneous and oral/mucosal manifestations of the cGvHD without an obvious sign of significant toxicity. Therefore, CMS believes that the evidence is sufficient to conclude that extracorporeal photopheresis will have health benefits for the treatment of Medicare patients with cGvHD that is refractory to increasing doses of standard immunosuppressive drugs. Based upon the above findings, extracorporeal photopheresis is reasonable and necessary for patients of any age with chronic graft versus host disease whose disease is refractory to standard immunosuppressive drug treatment.

3) Bullous Pemphigoid and Pemphigus Vulgaris

After a complete review of the scientific and clinical evidence regarding extracorporeal photopheresis for PV and BP there was a total of 17 patients. We find that there are very few patients and no control groups. Good data on survival in patients with BP or PV treated by extracorporeal photopheresis are not available. The data is sparse and poor. In the Wollina paper, the authors conclude the following: “short-time adjuvant ECP is a recommendable treatment modality for drug-resistant autoimmune bullous disease and prospective controlled trials comparing long-term and short-term adjuvant ECP in autoimmune bullous disease are necessary to validate our observations” (Wollina et al., 1999). The one review we found could not recommend extracorporeal photopheresis for PV or BP. Based on the available data, CMS has determined that there is insufficient evidence to conclude that extracorporeal photopheresis treatment for bullous pemphigoid and pemphigus vulgaris will improve health outcomes for Medicare patients in general without limitations. Therefore, CMS has determined that extracorporeal photopheresis is not reasonable and necessary for the treatment of bullous pemphigoid and pemphigus vulgaris.

IX. Decision

The Centers for Medicare and Medicaid Services (CMS) has determined that extracorporeal photopheresis is reasonable and necessary for:

1. Patients with acute cardiac allograft rejection whose disease is refractory to standard immunosuppressive drug treatment;
2. Patients with chronic graft versus host disease whose disease is refractory to standard immunosuppressive drug treatment.

CMS has determined that extracorporeal photopheresis is not reasonable and necessary for the treatment of bullous pemphigoid and pemphigus vulgaris.

All other indications remain non-covered.

Appendix A: General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine whether: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

CMS divides the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the relevance of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention’s risks and benefits.

The issues presented here represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has unique methodological aspects.

1. Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

• Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.

• Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.

• Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.

• Larger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.

• Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

• Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias)

• Co-interventions or provision of care apart from the intervention under evaluation (confounding)

• Differential assessment of outcome (detection bias)

• Occurrence and reporting of patients who do not complete the study (attrition bias)

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

• Randomized controlled trials

• Non-randomized controlled trials

• Prospective cohort studies

• Retrospective case control studies

• Cross-sectional studies

• Surveillance studies (e.g., using registries or surveys)

• Consecutive case series

• Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study's selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess the evidence.

2. Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens, and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease, and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing, and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage decisions for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation), and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations because one of the goals of our determination process is to assess health outcomes. We are interested in the results of changed patient management not just altered management. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

3. Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. For most determinations, CMS evaluates whether reported benefits translate into improved health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

Evidence Table [PDF, 152KB]

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[1] In a public comment the American College of Cardiology (ACC) noted that a new grading system for endomyocardial biopsies has been published and adopted to replace the Billingham classification. This new classification was published in the Journal of Heart and Lung Transplantation (Stewart, 2005). In response, CMS is aware of the new grading system; however, because the new grading system does not affect how we reviewed and interpreted the evidence regarding photopheresis, we will continue to use the Billingham classification.

Back to Top

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Back to Top